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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/063,514
Filing Date: May 01, 2002
Appellant(s): EATON ET AL.

AnneMarie Kaiser
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 02/24/2006 appealing from the Office action mailed 10/04/2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

The statement of the status of claims contained in the brief is correct.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. The amendment after final rejection filed on 12/29/2005 has been entered.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

Claims 14–17 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement because the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 14–17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Allman et al. BCL-6 expression during B-cell activation. Blood. 1996 Jun 15;87(12):5257-68.

Haynes et al. Proteome analysis: biological assay or data archive? Electrophoresis. 1998 Aug;19(11):1862-71.

Henikoff et al. Gene families: the taxonomy of protein paralogs and chimeras. Science. 1997 Oct 24;278(5338):609-14.

Hu et al. Analysis of genomic and proteomic data using advanced literature mining. J Proteome Res. 2003 Jul-Aug;2(4):405-12.

LaBaer J. Mining the literature and large datasets. Nat Biotechnol. 2003 Sep;21(9):976-7.

(9)(a) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 6, 7, 9 and 11–17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are directed to or encompass polypeptides comprising specifically recited fragments of the disclosed PRO874 polypeptide (SEQ ID NO: 10) and polypeptides having at least 95% amino acid sequence identity thereto. The specification characterizes the PRO874 polypeptide and polynucleotide as follows:

> [0036] FIG. 9 shows a nucleotide sequence (SEQ ID NO: 9) of a native sequence PRO874 cDNA, wherein SEQ ID NO: 9 is a clone designated herein as "DNA40621-1440".
>
> [0037] FIG. 10 shows the amino acid sequence (SEQ ID NO: 10) derived from the coding sequence of SEQ ID NO: 9 shown in FIG. 9. Page 11.
>
> DNA40621-1440 is more highly expressed in normal lung than as compared to lung tumor. Example 18, Page 141.

It is noted that the PRO874 polypeptide is less than a full length polypeptide because the amino acid sequence of SEQ ID NO: 10 does not begin with an initiator methionine (Figure 10).

Figure 10 also provides various structural features of the PRO874 polypeptide, presumably based on homology with domains of other known proteins. No further characterization is provided. One skilled in the art recognizes that although structural similarity can serve to classify a protein as related to other known proteins this classification is insufficient to establish a function or biological significance for the protein because ancient duplications and rearrangements of protein-coding segments have resulted in complex gene family relationships. Duplications can be tandem or dispersed and can involve entire coding regions or modules that

correspond to folded protein domains. As a result, gene products may acquire new specificities, altered recognition properties, or modified functions. Extreme proliferation of some families within an organism, perhaps at the expense of other families, may correspond to functional innovations during evolution. See Henikoff (Science. 1997 Oct 24;278(5338):609-14), page 609, Abstract. Accordingly, one skilled in the art would not accept mere homology as establishing a function of protein because gene products may acquire new specificities, altered recognition properties, or modified functions. Rather, homology complements experimental data accumulated for the homologous protein in understanding the homologous protein's biological role. Although, the presence of a protein module in a protein of interest adds potential insight into its function and guides experiments, insight into the biological function of a protein cannot be automated. However, homology can be used to guide further research. See Henikoff, paragraph bridging pages 613-614, through page 614, paragraph bridging columns 1-2.

No information is provided in the differential analysis of PRO874 mRNA expression regarding the level of expression, activity, or role in lung cancer of the PRO874 polypeptide. The specification fails to establish the correlation between the disclosed change in PRO874 mRNA expression and a change in PRO874 polypeptide expression in normal tissue *vs.* tumor tissue. Differential analysis of mRNA expression is not always correlated with protein levels. For example, Allman (Blood. 1996 Jun 15;87(12):5257-68) discloses that germinal center B cells express dramatically more BCL-6 protein than resting B cells, despite similar BCL-6 mRNA levels in the two cell populations. Page 5257, paragraph bridging left and right columns. mRNA translation is regulated in many genes and can be mediated by binding of proteins to cis-

acting RNA motifs in the untranslated regions of the mRNAs (paragraph bridging pages 5266-5267). Furthermore, Haynes (Electrophoresis. 1998 Aug;19(11):1862-71) states:

> "Interpretation of quantitative mRNA expression profiles frequently implicitly or explicitly assume that for specific genes the transcript levels are indicative of the levels of protein expression" (page 1863, left column, full paragraph 1),
>
> "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis" page 1863, right column, full paragraph 2).

In view of the fact that there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis, a skilled artisan would not know if the disclosed change in PRO874 mRNA expression is associated with a corresponding change in the level of PRO874 protein.

Furthermore, the specification's example 18 only presents data showing a relative difference in PRO874 mRNA levels. There is no evidence that PRO874 mRNA was highly expressed or highly under-expressed and Appellants have not provided any comparison of the levels of PRO874 polypeptide expression. The literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu (J Proteome Res. 2003 Jul-Aug;2(4):405-12) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (page 408, middle of right column). Hu discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease

(see discussion section). Hu also provides evidence that the skilled artisan recognizes that in differential analysis of mRNA expression there are biologically relevant results as well as biologically irrelevant results. See Hu, which teaches:

> "[h]igh-throughput technologies, such as proteomic screening and DNA micro-arrays, produce vast amounts of data requiring comprehensive analytical methods to decipher the biologically relevant results" (Abstract).
>
> "In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" (page 405, left column, full paragraph 1).
>
> "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful. ... For genes displaying a 5-fold change or less ... there was no evidence of a correlation between altered gene expression and a known role in the disease. This reflects ... genes whose modest changes in expression may be unrelated to the disease." Paragraph bridging pages 411-412.

Furthermore, LaBaer (Nat Biotechnol. 2003 Sep;21(9):976-7) teaches:

> In the accelerating quest for disease biomarkers, the use of high-throughput technologies, such as DNA microarrays and proteomics experiments, has produced vast datasets identifying thousands of genes whose expression patterns differ in diseased versus normal samples. Although many of these differences may reach statistical significance, they are not always biologically meaningful. For example, reports of mRNA or protein changes of as little as two-fold are not uncommon, and although some changes of this magnitude turn out to be important, most are attributable to disease-independent differences between the samples. Page 976, paragraph bridging middle and right columns.

A tumor-independent change in mRNA expression cannot be used as a disease marker. The significance or relevance of PRO874 mRNA expression to lung tumor cannot be ascertained because the skilled artisan would not know if the difference in PRO874 mRNA expression is tumor-dependent or tumor-independent, as supported by Hu and LaBaer. Even if one were to assume that the present results with PRO874 mRNA expression could reasonably be correlated

with an assumed change in PRO874 polypeptide expression, it still could not be ascertained if the assumed difference in PRO874 polypeptide expression is disease-dependent or disease-independent because one would not know if the difference in PRO874 mRNA expression is disease-dependent or disease-independent.

The specification does not teach the level of reproducibility or reliability of the results seen in Example 18. There are no absolute levels of PRO874 mRNA in control or tumor tissue disclosed. The likelihood that the level of PRO874 from a lung tissue sample from a patient with lung cancer would be higher or lower when compared with normal tissue is unknown. It is unknown how many samples would be needed or what sensitivity would be needed. Appellants only teach that PRO874 mRNA was "more highly expressed in" normal lung as compared to lung tumor, and this does not enable the skilled artisan to differentiate between expression levels in order to diagnose any diseases.

The instant claims encompass proteins of as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as PRO874 one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use it. Thus, there was no immediately apparent or "real world" utility for the PRO874 polypeptide as of the filing date. After further research, a specific and substantial utility might be found for the PRO874 polypeptide of the instant invention. This further characterization, however, is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete.

(10)(a) Response to Argument

Response to arguments at B.1.–B.5.

Appellants' discussion of the utility legal standard, burden of proof and standard of proof is acknowledged. However, the present rejection is based upon Appellants' failure to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Adopting Appellants' standard for utility would result in a per se rule that any disclosed difference in mRNA expression is significant, relevant, and tumor-dependent and that any such difference would require a per se rule of utility for the polynucleotide, the encoded polypeptide and antibodies thereto. The examiner declines to attenuate the utility requirement to this degree because this standard is not what the art teaches. The countervailing evidence shows that the skilled artisan would not know if the disclosed change in PRO874 transcripts is tumor-dependent or tumor-independent. See Hu and LaBaer, as discussed above. A tumor-independent detection of a change in mRNA expression cannot be used as a tumor marker. The skilled artisan would not know if or how expression of the PRO874 polypeptide would change in tumors because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis. See Haynes, as discussed above. This conclusion is supported by:

> Allman (Blood. 1996 Jun 15;87(12):5257-68):
>
> "germinal center B cells express dramatically more BCL-6 protein than resting B cells, despite similar BCL-6 mRNA levels in the two cell populations" (page 5257, paragraph bridging left and right columns);
>
> Molecular Biology of the Cell, 3rd ed. (Exhibit 1, 07/01/2005):
>
> "other controls can act later in the pathway from DNA to protein to modulate the amount of gene product that is made" (page 453, last full paragraph);
>
> Molecular Biology of the Cell, 4th ed. (Exhibit 4, 12/10/2004 and Exhibit 1, 07/01/2005):

> "the final level of a properly folded protein in a cell therefore depends upon the efficiency with which each of the many steps [from DNA to protein] is performed" (page 363, last full paragraph and page 364, Figure 6-90);
>
> Genes VI (Exhibit 3, 07/01/2005):
>
> "production of RNA cannot inevitably be equated with production of protein" (paragraph bridging pages 847-848).
>
> the declaration of Dr. Polakis under 37 CFR 1.132 (Exhibit 3, 12/10/2004):
>
> "... there have been published reports of genes for which such a correlation does not exist, ..." (paragraph 6);
>
> Meric (Mol Cancer Ther. 2002 Sep;1(11):971-9 (Exhibit 5, 07/01/2005):
>
> Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability. Page 971, left column, first paragraph of introduction.

See also the Polakis declaration (Exhibit 3, 12/10/2004) wherein it is taught that ~20% of the samples examined do not show a correlation between an increase in the level of mRNA and an increase in the level of the encoded protein (paragraph 5).

Even if one were to assume that the disclosed change in PRO874 transcripts could reasonably be correlated with an assumed change in PRO874 polypeptide expression the skilled artisan still would not know if the assumed change in PRO874 polypeptide expression is tumor-dependent or tumor-independent because it is unknown if the disclosed change in PRO874 transcripts is tumor-dependent or tumor-independent. Neither the specification nor any of Appellants' arguments, exhibits, declarations or other evidence provide any specific data disclosing if or how PRO874 polypeptide expression changes in tumor tissue. Instead, Appellants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO874 transcripts and PRO874

polypeptide expression to argue that it is more likely than not that a change in PRO874 transcripts is correlated with an assumed change in PRO874 polypeptide expression. Without any evidence of the expression of PRO874 in tumor tissue or normal tissue this argument is of no avail to Appellants.

The asserted utility of the claimed polypeptides would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Regarding the requirement for further experimentation as a basis for lack of utility, utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities (M.P.E.P. § 2107.01 I). In the present case, the asserted diagnostic or therapeutic utilities of the PRO874 gene, polypeptide and antibodies would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use because the skilled artisan would not know if or how PRO874 polypeptide expression, or expression of any of the other claimed polypeptides, would change in tumors.

Unlike the situations wherein a claimed compound has been tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient under the patent laws, or wherein an invention has only limited utility and is only operable in certain applications and therefore has some degree of utility sufficient for patentability, in the present situation Appellants have not provided any testing of the expression of the PRO874 polypeptide. In the absence of any information on the role, activity or expression of the PRO874 polypeptide in cancer, the examiner therefore considers the asserted utilities to not be specific and substantial because the skilled artisan would not know if the reported change in PRO874 transcripts is tumor-dependent or tumor-independent and would not know if or how PRO874 polypeptide

expression would change in cancer. Although the asserted utility may be specific to the claimed invention, it is not substantial. Therefore, the claimed invention lacks a specific and substantial asserted utility.

Appellants' utility standard would mandate only a showing that it is "not implausible" that the invention will work for its intended purpose. If mere plausibility were the test for how to use a claimed invention, Appellants could obtain patent rights to "inventions" based on a disclosure consisting of little more than guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor disclose how to use an invention rather than merely proposing an unproved hypothesis. As set forth in Brenner v. Manson:

> But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. "[A] patent system must be related to the world of commerce rather than to the realm of philosophy."

There is a complete absence of data supporting the statements which set forth the desired results of the claimed invention and the countervailing evidence shows that the skilled artisan would not know if the disclosed change in PRO874 transcripts is tumor-dependent or tumor-independent and would not know if or how expression of the PRO874 polypeptide would change in tumors.

Appellants are not being asked to prove the asserted diagnostic utility either as a matter of statistical certainty or beyond a reasonable doubt. Rather, the facts to be established are, is the reported change in PRO874 transcripts tumor-dependent or tumor-independent and, if the reported change is tumor-dependent, is there a corresponding change in PRO874 polypeptide

expression. The specification does not establish if the disclosed change in PRO874 mRNA expression is one of those cases where there is a correlation between mRNA expression and polypeptide expression. Appellants have not provided any testing of PRO874 polypeptide expression. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO874 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO874 polypeptide, the specification does not provide some immediate benefit to the public for the PRO874 polypeptide. None of Appellants' exhibits, arguments or declarations establish if or how expression of the PRO874 polypeptide changes in tumor tissue as compared to normal tissue. Instead, Appellants merely propose a utility that is "not implausible," relying on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO874 mRNA expression and PRO874 polypeptide expression without any evidence of the expression level of the PRO874 polypeptide in tumor tissue or normal tissue. See, e.g., Brenner, 383 U.S. at 534, 148 USPQ at 695 (An invention does not have utility sufficient to satisfy § 101 until it is "refined and developed" to the point of providing a specific benefit in currently available form.).

The following passages from the specification seem most relevant for construing the asserted diagnostic utility:

> [0336] The PRO polypeptides and nucleic acid molecules of the present invention may also be used diagnostically for tissue typing, wherein the PRO polypeptides of the present invention may be differentially expressed in one tissue as compared to another, preferably in a diseased tissue as compared to a normal tissue of the same tissue type. PRO nucleic acid molecules will find use for generating probes for PCR, Northern analysis, Southern analysis and Western analysis. Page 93.
>
> [0407] The anti-PRO antibodies of the invention have various utilities. For example, anti-PRO antibodies may be used in diagnostic assays for PRO, e.g., detecting its expression (and in some cases, differential expression) in

> specific cells, tissues, or serum. Page 112.
>
> [0530] Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. These assays provided the following results. Page 140.

The specification does not make a specific assertion regarding positive correlations between PRO874 mRNA expression and PRO874 polypeptide expression, i.e., if PRO874 mRNA is up-regulated, PRO874 polypeptide is up-regulated or *vice versa*. The correlation between the disclosed change in PRO874 mRNA expression and a change in PRO874 polypeptide expression is unknown and is not disclosed. In fact, Appellants argue that a necessary correlation between gene expression and protein expression is not required to establish utility. See the response filed 12/10/2004 at page 16, last full paragraph. The second Grimaldi declaration filed (Exhibit 2, 12/10/2004) asserts that:

> " ... even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy." Paragraph 6.

The Ashkenazi declaration filed (Exhibit 6, 12/10/2004) asserts that:

> "absence of gene product overexpression still provides significant information for cancer diagnosis and treatment." Paragraph 6.

Appellants are arguing that whatever the expression level and whatever the correlation, the PRO874 polypeptide is useful because skilled artisans could figure out for themselves what any observed experimental result might mean. The specification does not disclose anything regarding "more accurate tumor classification." The examiner does not agree that such a

disclosure provides a "specific benefit in currently available form" because the expression of all polynucleotides or polypeptides from a tumor sample can invariably be classified as either increased, decreased, non-existent, or unchanged as compared to some standard level of expression. It can then be asserted that all proteins or polynucleotides that are expressed in this manner can be used to detect or characterize the tumor. Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific nor a substantial utility.

There is a complete absence of data supporting the statements which set forth the desired results of the claimed invention and the countervailing evidence shows that the skilled artisan would not know if the disclosed change in PRO874 transcripts is tumor-dependent or tumor-independent and would not know if or how expression of the PRO874 polypeptide would change in tumors. The specification fails to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Therefore, the disclosure that PRO874 mRNA is differentially expressed in normal tissue as compared to tumor tissue does not impute a specific and substantial utility to the PRO874 polypeptide. Based on the present disclosure, one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context of use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Thus, the present disclosure is simply a starting point for further research and investigation into potential practical uses of the claimed polynucleotides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Response to arguments at 6.a.

Appellants argue that the data in Example 18 and the first Grimaldi declaration (Exhibit 1, 12/10/2004) are sufficient to establish the asserted diagnostic utility, and the examiner has not rebutted the presumption of utility afforded Appellants' application. Appellants argue that the first Grimaldi declaration provides further facts relating to example 18, in that the DNA libraries used in the gene expression studies were made from pooled samples. Appellants argue that the PTO has not supplied any reasons or evidence to question the first Grimaldi declaration. Appellants remind the examiner that Office personnel must accept an opinion from a qualified expert. Appellants' arguments have been fully considered but they are not persuasive.

The MPEP makes clear, "factual evidence is preferable to opinion testimony ... ." The MPEP also makes clear, "opinion" testimony is entitled to be considered, i.e., it is "admissible" in an ex parte proceeding. MPEP §716.01(c). The mere fact that opinion testimony is admissible (i.e., is entitled to be considered) does not per se mean it must be accorded controlling weight. In assessing the weight to be given expert testimony in an ex parte context, the examiner may properly consider, among other things:

(1) The nature of the fact sought to be established.

(2) The strength of any opposing evidence.

(3) The interest of the expert in the outcome of the case.

(4) The presence or absence of factual support for the expert's opinion.

Unless an "expert" states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight.

The first Grimaldi declaration (Exhibit 1, 12/10/2004) has been considered. However, the assertions that "Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual" (paragraph 5), "it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA" (paragraph 6), "The precise levels of gene expression are irrelevant" (paragraph 7), and "If a difference is detected, ... the gene and its corresponding polypeptide ... are useful for diagnostic purposes" (paragraph 7) are conclusory and unsupported.

Although the declaration states that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues, this statement is in contrast to the specification's teachings, which discloses:

> Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. Page 140, paragraph 0530.

It is unknown what level of difference is being reported or how many samples were tested. The declaration does not provide anything specific concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. Given the paucity of information regarding PRO874 mRNA expression and the complete lack of

data concerning PRO874 polypeptide expression, Hu and LaBaer are evidence that a skilled artisan would consider the precise level of PRO874 gene expression as relevant.

The asserted diagnostic utility of the PRO874 polypeptide depends upon its ability to differentiate normal tissue from tumor tissue. In practicing the invention some value for PRO874 polypeptide expression must be obtained in order to make this distinction. Establishing a cutoff value for this distinction would be difficult unless one knows the degree of variation within the pool, which Appellants have not provided. There is no evidence of record concerning the normal range of PRO874 mRNA levels or PRO874 polypeptide levels in normal tissue or tumor tissue. There is no evidence of record that a normal range of PRO874 mRNA or PRO874 polypeptide levels could be defined that would distinguish normal tissue from tumor tissue. Without a knowledge of the variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue. Pooled samples would also obscure the variation between samples, making the disclosed results for PRO874 polynucleotide expression less useful, accurate and informative than if results from individual samples had been provided. In fact the range of values from normal and/or tumor tissue could be so broad that it would be impossible to distinguish normal tissue from tumor tissue.

Appellants argue that Hu or LaBaer reflect a bias in the literature and reflect nothing regarding the ability of gene that is at least 2-fold differentially expressed to serve as a disease marker. Appellants argue that Hu or LaBaer's methodology provides little or no information regarding the ability of genes with less than a 5-fold difference in expression to serve as a disease marker. Applicant's arguments have been fully considered but they are not persuasive. Hu and LaBaer developed MedGene as a means for evaluating and validating large data sets of

gene expression data. MedGene is not limited to any specific relationship type, but rather encompasses all reported gene-disease links. See LaBaer, page 977, leftmost column. Bias or no bias, a gene whose change in expression is attributable to disease-independent differences between the samples cannot be used as a diagnostic indicator of the disease. Although Hu indicates that the observed correlation was only found among ER-positive tumors, not ER-negative, Hu's approach identified a set of relatively understudied, yet highly expressed genes in ER-negative tumors that are worthy of further examination. This is consistent with Hu's conclusion that even when expression changes as small as 2-fold are statistically significant, it is not always clear if they are biologically meaningful. These small changes in expression may reflect genes whose role in cancer may not involve large changes in expression or genes whose modest changes in expression may be unrelated to the disease. The alleged bias does not vitiate the finding that mRNA or protein changes of as little as two-fold are not uncommon, and although some changes of this magnitude turn out to be important, most are attributable to disease-independent differences between the samples. There is no evidence of record that PRO874 transcripts are either highly expressed or highly under-expressed or that the reported change in PRO874 transcripts is consistent, reliable and measurable. There is a total lack of data concerning PRO874 polypeptide expression.

Appellants argue that Hu and LaBaer are not relevant to the present application, which does not rely on microarray data. Appellants argue that the microarray technique is not as accurate as the RT-PCR method used by Appellants. Appellants' arguments have been fully considered but they are not persuasive because they are conclusory and unsupported. The examiner concludes Appellants arguments are mere argument.

The examiner has addressed Appellants' comments regarding the accuracy of pooled samples, above.

Appellants argue that genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. Appellants' arguments have been fully considered but they are not persuasive. Appellants have not provided any evidence that the observed change in PRO874 transcripts was reliable, consistent or reproducible.

The examiner does not and has not asserted or required that one must know what role a gene or polypeptide plays in cancer for it to have utility. The examiner did assert that the specification does not provide any information regarding the expression, role, or activity of the PRO874 polypeptide in cancer.

Appellants' arguments regarding Wang (Trends Pharmacol Sci. 1996 Aug;17(8):276-9) have been considered. However, the examiner is no longer relying upon Wang.

Response to arguments at 6.b.

Appellants argue that neither Haynes nor Gygi looked at whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Appellants argue that Haynes and Gygi are irrelevant to Appellants' assertions. Appellants argue that the examiner's interpretation is inconsistent with Haynes and Gygi. Appellants argue that neither Haynes nor Gygi address Appellants' assertion that generally, changes in mRNA level for a particular gene lead to changes in the level of the encoded protein. Appellants' arguments have been fully considered but they are not persuasive. Appellants have not examined whether the reported change in PRO874 transcripts is correlated with a corresponding change in PRO874

polypeptide expression. It is further noted that Appellants' differential analysis is based upon comparing the steady-state levels of PRO transcripts in one or more normal tissues with the steady state levels of PRO transcripts in one or more tumor tissues. See the specification at page 140, paragraph 0530:

> Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor.

Appellants assume that PRO874 transcript levels are indicative PRO874 polypeptide levels. The specification fails to provide any testing of PRO874 polypeptide levels. Haynes teaches:

> "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis" (page 1863, right column, full paragraph 2).
>
> "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts." Page 1870 left column, last full paragraph;

Because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis the skilled artisan would not know if the disclosed change in PRO874 mRNA transcripts is associated with a corresponding change in the level of PRO874 protein. Hence, the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer. This conclusion is supported by Allman (Blood. 1996 Jun 15;87(12):5257-68), Molecular Biology of the Cell, 3rd

ed. (Exhibit 1, 07/01/2005), Molecular Biology of the Cell, 4th ed. (Exhibit 4, 12/10/2004 and Exhibit 1, 07/01/2005), Genes VI (Exhibit 3, 07/01/2005), the Polakis declaration (Exhibit 3, 12/10/2004), and Meric (Mol Cancer Ther. 2002 Sep;1(11):971-9) (Exhibit 5, 07/01/2005), as discussed above.

Regarding Allman, Appellants argue that an observed change protein level without a corresponding change in mRNA level is not contrary to Appellants' assertion, and evidence of changes in protein levels when mRNA levels are unchanged has no relevance to Appellants' assertion. Appellants argue that Allman supports Appellants' position because Allman's results were unanticipated. Applicant's arguments have been fully considered but they are not persuasive. If one is to argue, as Appellants have argued, that because PRO874 transcripts are differentially expressed in tumors it is more likely than not that the PRO874 polypeptide is similarly differentially expressed in tumors, and therefore the PRO874 polypeptide and antibodies can be used for tumor diagnosis, then one must also accept the argument that because resting B cells and germinal center B cells express similar BCL-6 mRNA levels it is more likely than not that the BCL-6 protein is not differentially expressed in these two cell populations, and therefore the BCL-6 protein and antibodies thereto cannot be used as a marker for germinal center B cells. One must also accept the argument that because germinal center B-cells express dramatically more BCL-6 protein than resting B cells it is more likely than not that BCL-6 mRNA is differentially expressed in these two cell populations, and therefore BCL-6 mRNA can be used as a marker for germinal center B-cells. Allman indicates that this is not so and therefore Allman does not support Appellants' position. The fact that it was unexpected that increases in BCL-6 protein were not correlated with a corresponding change in the level of BCL-

6 mRNA only establishes that the skilled artisan would not know if or how PRO874 polypeptide expression changes in tumors. To argue that Allman supports Appellants' position because Allman did not obtain the anticipated results is akin to arguing that the skilled artisan could experiment with PRO874 mRNA and polypeptide levels and determine for themselves how to use the claimed invention. Unlike Allman, Appellants have not provided any testing of the role, activity or expression of the PRO874 polypeptide.

Response to arguments at 6.c.

Appellants' arguments regarding Yousef have been considered. The examiner agrees that it is difficult to determine what standard of usefulness Yousef is applying when on the one hand he says that "hK6, hK10 and hK11 are useful serological diagnostic markers for ovarian cancer because their serum levels are higher than normal in >50% of ovarian cancer patients" (page 2226, left column, full paragraph 1) and on the other hand he says "Further experimentation is necessary to establish the usefulness of these KLKs for diagnosis, prognosis, and treatment of cancer" (page 2226, right column, last paragraph). The examiner no longer relies on Yousef.

Appellants argue that the caveat in example 12 does not require reproducibility or reliability. Appellants argue that it is inappropriate to require statistical certainty because the appropriate standard is "more likely than not true." Appellants' arguments have been fully considered but they are not persuasive. Unlike the situation wherein the specification discloses that receptor A is present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells, in the present case Appellants rely on a qualitative comparison of PRO874 mRNA expression between tumor tissue and normal samples in order to establish utility for the presently claimed polypeptides. However, Appellants have not looked at whether

the reported change in the transcript level for the PRO874 gene leads to a change in the level of expression of the PRO874 polypeptide. Furthermore, a skilled artisan would not know if the reported change in PRO874 transcripts is disease-dependent or disease-independent. Even if the examiner were to assume that the change in PRO874 mRNA transcripts could reasonably be correlated with an assumed change in PRO874 polypeptide expression, it still could not be ascertained if the assumed change in PRO874 polypeptide expression would be disease-dependent or disease-independent because the skilled artisan would not know if the change in PRO874 transcripts is disease-dependent or disease-independent. The specification lacks a sufficient correlation between the test performed on PRO874 transcripts and the asserted utility of the PRO874 polypeptide. Because Appellants have failed to establish any correlation between PRO874 mRNA expression and PRO874 polypeptide expression in normal tissue or tumor tissue Appellants have failed to establish a significant probability that PRO874 polypeptide is useful as a cancer diagnostic or therapeutic. There is no reason for the skilled artisan to believe that it is more likely than not that the claimed polypeptides could be used as a cancer diagnostic or therapeutic. Appellants are the ones arguing that the first Grimaldi declaration establishes that the data in Example 18 are reproducible, reliable, and significant enough. See page 42, full paragraph 2 and page 44, full paragraph 1 of the appeal brief. There is no evidence of record that data in Example 18 are consistent, reproducible, or reliable. Although the reported change in PRO874 mRNA may be significant, it is unknown what level of difference is being reported and whether these changes are tumor-dependent or tumor-independent.

Response to arguments at 6.d.

This is a summary of Appellants' previous arguments to which the examiner has already responded.

Response to arguments at 7.a. and 8.a.

The examiner has already responded to Appellants' arguments regarding the data in example 18 and the first Grimaldi declaration, above.

Response to arguments at 7.b., 7.c, and 8.b-8.g.

Appellants argue that they have established that the accepted understanding in the art is that there is a reasonable correlation between the level of mRNA and the level of the encoded protein. Appellants argue that it is well established that a change in the level of mRNA generally leads to a change in the level of the corresponding protein. Appellants argue that the second Grimaldi declaration (Exhibit 2, 12/10/2004) and the Polakis declaration (Exhibit 3, 12/10/2004), as supported by Molecular Biology of the Cell, 3rd ed. (Exhibit 1, 07/01/2005), Molecular Biology of the Cell, 4th ed. (Exhibit 4, 12/10/2004 and Exhibit 1, 07/01/2005), as further supported by Genes VI (Exhibit 3, 07/01/2005), and as additionally supported by Zhigang (Exhibit 4, 07/01/2005) and Meric (Exhibit 5, 07/01/2005), establish that there is a positive correlation between changes in mRNA levels and changes in the corresponding protein levels. Appellants' arguments have been fully considered but they are not persuasive. Appellants assume that the reported change in PRO874 mRNA transcripts is associated with a corresponding change in PRO874 polypeptide expression. Haynes, Allman, the Polakis declaration, Molecular Biology of the Cell, 3rd ed., Molecular Biology of the Cell, 4th ed., Genes VI, and Meric are evidence that the skilled artisan would not know if or how PRO874 polypeptide levels would change in tumors, as discussed above.

The second Grimaldi declaration (Exhibit 2, 12/10/2004) has been considered. The MPEP makes clear, "factual evidence is preferable to opinion testimony ... ." The MPEP also makes clear, "opinion" testimony is entitled to be considered, i.e., it is "admissible" in an ex parte proceeding. MPEP §716.01(c). The mere fact that opinion testimony is admissible (i.e., is entitled to be considered) does not per se mean it must be accorded controlling weight. In assessing the weight to be given expert testimony in an ex parte context, the examiner may properly consider, among other things:

(1) The nature of the fact sought to be established.

(2) The strength of any opposing evidence.

(3) The interest of the expert in the outcome of the case.

(4) The presence or absence of factual support for the expert's opinion.

Unless an "expert" states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight.

The facts to be established are whether or not the disclosed change in PRO874 transcripts is disease-dependent or disease-independent and whether or not there is a positive correlation between the reported change in PRO874 transcripts and a change in PRO874 polypeptides levels in tumors as compared to their normal tissue counterparts. In the present case it is unknown if the reported change in PRO874 mRNA expression is tumor-dependent or tumor-independent. The declaration does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA

levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the Polakis declaration (Exhibit 3, 12/10/2004). The assertion that PRO874 polypeptide expression is useful regardless of the correlation between PRO874 mRNA expression and PRO874 polypeptide expression because it would allow more accurate tumor classification is akin to asserting that whatever the expression level and whatever the correlation, the PRO874 polypeptide and antibodies are useful because skilled artisans could figure out for themselves what any observed experimental result might mean. The specification does not disclose anything regarding "more accurate tumor classification." The examiner does not agree that such a disclosure provides a "specific benefit in currently available form" because the expression of all polynucleotides or polypeptides from a tumor sample can invariably be classified as either increased, decreased, non-existent or unchanged as compared to some standard level of expression. It can then be asserted that all proteins or polynucleotides that are expressed in this manner can be used to detect, characterize or classify the tumor. Such an asserted utility is not specific to the PRO874 gene or polypeptide and is analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility. Unlike the situation in Grimaldi (Blood. 1989 Jun;73(8):2081-5), wherein chromosomal translocations have proven to be important markers of the genetic abnormalities central to the pathogenesis of cancer, there is no evidence that the present situation involves the cloning of a chromosomal breakpoint. Unlike Meeker (Blood. 1990 Jul 15;76(2):285-9) or Singleton (Pathol Annu. 1992;27 Pt 1:165-90), Appellants have not

provided any testing of the level of expression, activity, or role in cancer of the PRO874 polypeptide.

The examiner has already responded to Appellants' arguments regarding the caveat in example 12 of the utility guidelines, above.

The Polakis declaration (Exhibit 3, 12/10/2004) has been considered. The MPEP makes clear, "factual evidence is preferable to opinion testimony ... ." The MPEP also makes clear, "opinion" testimony is entitled to be considered, i.e., it is "admissible" in an ex parte proceeding. MPEP §716.01(c). The mere fact that opinion testimony is admissible (i.e., is entitled to be considered) does not per se mean it must be accorded controlling weight. In assessing the weight to be given expert testimony in an ex parte context, the examiner may properly consider, among other things:

(1) The nature of the fact sought to be established.

(2) The strength of any opposing evidence.

(3) The interest of the expert in the outcome of the case.

(4) The presence or absence of factual support for the expert's opinion.

Unless an "expert" states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight.

The facts to be established are whether or not the disclosed change in PRO874 transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO874 transcripts and a corresponding change in PRO874 polypeptides levels. The declaration does not provide any data concerning PRO874 mRNA expression,

PRO874 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. Given the paucity of information regarding PRO874 expression in tumors and the evidence in the art that there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis, one skilled in the art would not know if the change in PRO874 mRNA expression was disease-dependent or disease-independent, would not know if or how PRO874 polypeptide expression would change in tumors, and would have a reasonable, legitimate basis to doubt the utility of the PRO874 polypeptide. Even if the examiner were to assume that the disclosed change in PRO874 transcripts could reasonably be correlated with an assumed change in PRO874 polypeptide expression, it still could not be ascertained if the assumed change in PRO874 polypeptide expression would be disease-dependent or disease-independent because it is unknown if the change in PRO874 transcripts is disease-dependent or disease-independent. While Dr. Polakis refers to his experiments, only conclusions were set forth in the declaration. No data or results were presented for independent analysis. Even if the examiner were to accept Dr. Polakis' conclusion, it still would be considered evidence that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer because 20% of the cases examined do not show a correlation, according to Dr. Polakis. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to Dr. Polakis.

Appellants emphasize that they do not need to prove an exact or absolute correlation between changes in mRNA and changes in protein levels. Appellants' arguments have been fully considered but they are not persuasive. The examiner considers these arguments somewhat misleading because Appellants have never been asked prove such an exact or absolute correlation. Nor have Appellants been required to establish the asserted diagnostic utility as a matter of absolute or statistical certainty, as discussed above. Rather, the facts to be established are whether or not the disclosed change in PRO874 transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO874 transcripts and a corresponding change in PRO874 polypeptides levels.

Molecular Biology of the Cell (Exhibit 1, 07/01/2005 and Exhibit 4, 12/10/2004 and Exhibit 1, 07/01/2005), Genes VI (Exhibit 3, 07/01/2005), Zhigang (Exhibit 4, 07/01/2005), and Meric (Exhibit 5, 07/01/2005) are acknowledged. However, Molecular Biology of the Cell (Exhibit 1, 07/01/2005) acknowledges that "other controls can act later in the pathway from DNA to protein to modulate the amount of gene product that is made" (page 453, last full paragraph). Molecular Biology of the Cell (Exhibit 4, 12/10/2004 and Exhibit 1, 07/01/2005) acknowledges that the final level of protein depends upon the efficiency with which each of the many steps from DNA to protein is performed (page 363, last full paragraph and page 364, Figure 6-90). Genes VI (Exhibit 3, 07/01/2005) acknowledges that "production of RNA cannot inevitably be equated with production of protein" (paragraph bridging pages 847-848). Molecular Biology of the Cell and Genes VI support and are consistent with the examiner's position that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer and that the present application fails to disclose to disclose enough information

about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The examiner does not agree that Figure 6-3, page 302 (Exhibit 4, 12/10/2004 and Exhibit 1, 07/01/2005) illustrates a basic principle that there is a correlation between increased gene expression and increased protein expression. This figure only illustrates that different genes can be expressed with different efficiencies.

Regarding Zhigang (Exhibit 4, 07/01/2005), Appellants argue that statistical certainty is not a requirement, and that the PTO is requiring statistical certainty. Applicant's arguments have been fully considered but they are not persuasive. It is acknowledged that Zhigang presents data showing a high degree of correlation between PSCA protein and mRNA expression (page 4 of 7, right column, last sentence). However, exceptions were noted (paragraph bridging pages 3 of 7 and 4 of 7; page 4 of 7, left column, full paragraph 1). Thus, Zhigang supports and is consistent with the examiner's position that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The examiner is not requiring statistical certainty. Unlike Zhigang, Appellants have not provided any testing of the PRO874 polypeptide. Zhigang does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. The fact that there may be a general correlation does not tell the skilled artisan if the reported change in PRO874 transcripts is disease-dependent or disease-independent and does not tell the skilled artisan if or how PRO874 polypeptide expression changes.

Regarding Meric (Exhibit 5, 07/01/2005), Appellants do not assert that transcriptional levels are the only factor in determining polypeptide levels. Appellants assert that changes in mRNA levels are generally indicative of changes in polypeptide levels. Applicant's arguments have been fully considered but they are not persuasive. Meric states that the "fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells" (page 971, right column, first paragraph of "Introduction"). However, the present specification does not provide any testing of the level of expression, activity, or role in cancer of the PRO874 polypeptide. Therefore, the difference in PRO874 polypeptide expression between cancer cells and normal cells is unknown, and thus not exploitable. Meric also acknowledges that several alterations in translational control occur in cancer (page 971, Abstract) and that gene expression is quite complicated (page 971, right column, first paragraph of "Introduction"), suggesting that protein levels can be modulated independently of the level of mRNA. Thus, Meric supports and is consistent with the examiner's position that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The fact that one of skill in the art can potentially exploit the differences in gene expression between cancer cells and normal cells does not tell the skilled artisan if the reported change in PRO874 transcripts is disease-dependent or disease-independent and does not tell the skilled artisan if or how PRO874 polypeptide expression changes in tumor tissue.

Unlike Yousef, Appellants have not tested whether the reported change in the level of PRO874 mRNA is associated with a corresponding change in the level of the PRO874 polypeptide.

Response to arguments at 9.

The examiner has already responded to Appellants' discussion of the utility legal standard, burden of proof and standard of proof, above.

Response to arguments at 10.

Appellants' conclusion regarding the utility of the claimed invention has been considered but it is not persuasive. In the present case, the differential analysis of PRO874 transcripts does not prove that the PRO874 polypeptide will perform as a cancer diagnostic or therapeutic. The differential expression of the PRO874 polynucleotide has not been adequately correlated with the contemplated cancer diagnostics or therapeutics of the PRO874 polypeptide or antibodies. The PRO874 polynucleotide and polypeptide have not been tested to the extent that utility would be known to those of skill in the art.

(9)(b) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 6, 7, 9 and 11–17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(10)(b) Response to Argument

Appellants argue that they have established a substantial, specific, and credible utility for the claimed polypeptides. Appellants' arguments have been fully considered but they are not persuasive. As Appellants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

(9)(c) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 14–17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 14-17 recite the limitation "wherein said polypeptide ... can be used to generate an antibody ... ." These claims encompass any and all antigenically cross-reactive polypeptides

possessing the recited percent identity, regardless of their biological activity. To obtain a valid patent, a patent application must be filed that contains a full and clear disclosure of the invention in the manner prescribed by 35 U.S.C. 112, first paragraph. The requirement for an adequate disclosure ensures that the public receives something in return for the exclusionary rights that are granted to the inventor by a patent. If mere antigenic cross-reactivity were the test for enablement under § 112, Appellants could obtain patent rights that may confer power to block off whole areas of scientific development related to the biologic activity of the polypeptide, for which Appellants have not provided any disclosure. It is entirely unclear why the disclosure of a single polypeptide, i.e., PRO874 (SEQ ID NO: 10), which is ideally suited to the making of antibodies to itself, would enable any and all antigenically cross-reactive polypeptides possessing the recited percent identity and possessing unknown and undisclosed biologic activities, when the specification provides no disclosure of any biological activity. Therefore, the scope of enablement provided to the skilled artisan by the disclosure is not commensurate with the scope of protection sought by the claims.

(10)(c) Response to Argument

Appellants argue that the examiner has failed to establish a *prima facie* case for rejecting the claims as lacking enablement because the standard for enablement is based on undue experimentation. Appellants argue that the examiner failed to make any specific findings of fact. Appellants argue that the power to block off whole areas of scientific development is not the test for enablement. Appellants argue that disclosure of a biological activity is not required for a skilled artisan to make or use the claimed polypeptides. Appellants argue that disclosure of a single polypeptide cannot support a rejection for lack of enablement. Appellants argue that the

specification teaches how to make the claimed polypeptides and antibodies that bind thereto. Appellants argue that the specification provides sufficient guidance as to how to use the claimed polypeptides. Appellants argue that the examiner impermissibly relies upon his personal opinion.

Appellants' arguments have been fully considered but they are not persuasive. All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims. The specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO, as indicated below:

> "Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO. Page 39, paragraph 0231.

Therefore, the claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity to the amino acid sequence of SEQ ID NO: 10, and possessing any and/or all underlying biological activities. The level of experimentation required to make and use such an invention is clearly beyond the level of enablement provided by the specification because the specification provides no disclosure of any biological activity of the native or naturally-occurring PRO874 polypeptide SEQ ID NO: 10.

Furthermore, an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 10 in lung samples is essential to appellants' claimed genus of variant polypeptides. The specification defines antibody specificity as follows:

> An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247.

The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The obvious choice is to use the polypeptide itself. The level of ingenuity required to make such an invention is clearly beyond that to be expected of skilled artisans. The specification does not disclose how this would be accomplished. Note that the claims are not limited to fusion proteins. Rather the claims encompass polypeptides that vary anywhere and everywhere from SEQ ID NO: 10, within the metes and bounds of the recited percent identity. After reading the specification, a person of skill in the art would not understand how to make the claimed genus, except for the native, naturally-occurring PRO874 polypeptide (SEQ ID NO: 10).

The examiner has provided sufficient evidence and reasoning to make a *prima facie* showing that appellants' disclosure is not commensurate in scope with the claimed invention, which requires antibodies that "specifically detect the polypeptide of SEQ ID NO: 10 in lung tissue."

Appellants separately argue that claim 15 is enabled for the same reasons that claims 14, 16, and 17 are enabled. Appellants further argue that the scope of claim 15 is narrower than that of claim 14, and thus less experimentation will be required to make these polypeptides.

Appellants argue that a skilled artisan would clearly be able to use these polypeptides. Appellants' arguments have been fully considered but they are not persuasive. Claim 15 is not enabled for the same reasons claim 14 is not enabled, as discussed above. Although the polypeptides of claim 15 are 99% identical to SEQ ID NO: 10, the level of experimentation required to make and use such an invention is still clearly beyond the level of enablement provided by the specification because the specification provides no disclosure of any biological activity. Furthermore, the state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant.

(9)(d) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 14–17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 14-17 recite the limitation "wherein said polypeptide ... can be used to generate an antibody ... ." These claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity, regardless of their biological activity. Appellants have not described the biologic activity of the PRO874 polypeptide or any of its variants. It is entirely unclear why the disclosure of a single polypeptide, i.e., PRO874, which is ideally suited to the making of antibodies to itself, would describe any and all antigenically cross-reactive

polypeptides possessing the recited percent identity and possessing unknown and undisclosed biologic activities, when the specification does not describe any biological activity. Therefore, the claimed subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(10)(d) Response to Argument

Appellants argue that the examiner has not provided any reasoning or evidence as to how the absence of the disclosure of a biological activity results in a lack of written description. Appellants argue that there is no substantial variation within the genus and that appellants were in possession of the common attributes or features of the claimed invention. Appellants argue that the claims are analogous to Example 14 of the written description guidelines because it was well known in the art how to make polypeptides having the recited percent identity, as evidenced by the specification at paragraphs 0256-0271, and because the specification discloses how to make antibodies that detect a particular PRO polypeptide and how to use them, as evidenced by the specification at paragraphs 0363-0379, 0407 and 0493-0499. Appellants argue that the function of producing an antibody specific to SEQ ID NO: 10 is directly related to the structure of the claimed polypeptides. Appellants argue that example 14 of the written description guidelines extends to all situations where the polypeptide is useful and there is no substantial variation within the genus. Appellants argue that claims 14–17 must share a particular biologic activity which restricts the amount of permissible structural variation within the genus. Appellants argue that the premise that a large genus cannot be described by a single species is wrong. Appellants argue that the facts in *Wallach* are very similar to the present case.

Appellants argue that it is routine to make the claimed variant polypeptides and is just as predictable and easy as creating all the nucleic acid molecules that encode a particular amino acid sequence. Appellants argue that it well within the purview of skilled artisans to determine which polypeptides can be used to make the recited antibodies. Appellants argue that the predictability of this structure/function combination is sufficient to put appellants in possession of the claimed invention.

Appellants' arguments have been fully considered but they are not persuasive. The specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO, as indicated below:

> "Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO. Page 39, paragraph 0231.

Therefore, the claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity to the amino acid sequence of SEQ ID NO: 10, and possessing any and/or all underlying biological activities. However, the specification does not describe any biological activity of the native or naturally-occurring PRO874 polypeptide SEQ ID NO: 10.

The examiner disagrees with the premise that making the claimed variant polypeptides and is just as predictable and easy as creating all the nucleic acid molecules that encode a particular amino acid sequence. All nucleic acid molecules that encode a particular amino acid sequence all share the same property of encoding that amino acid sequence. The nature, type and

number of nucleotide changes are discernable and predictable. However, the claimed variant polypeptides are all different polypeptides. The claims encompass polypeptides that vary anywhere and everywhere from SEQ ID NO: 10, within the metes and bounds of the recited percent identity. Note that the claims are not limited to fusion proteins. Unlike a biological activity, which imposes limitations on the nature, type and number of amino acid changes, the functional property of "can be used to generate an antibody ... to specially detect the polypeptide of SEQ ID NO: 10" does not limit the variation in the structure SEQ ID NO: 10 — the structure of the claimed variants — in any discernable, predictable or disclosed manner. Because the specification does not describe any biological activity of the claimed polypeptides and because the claims are not limited to any specific biologic activity of the claimed polypeptides, the present claims are not analogous to example 14 of the written description guidelines. Furthermore, an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 10 in lung samples is essential to appellants' claimed genus of variant polypeptides. The specification defines antibody specificity as follows:

> An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247.

The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The obvious choice is to use the polypeptide itself. Therefore, the function of the claimed variants is not related to the structure of the claimed variants. After reading the specification, a person of skill in the art would not understand Appellants to have invented a polypeptide having the recited percent identity that can be used to make an antibody which can be used to specifically detect the

polypeptide of SEQ ID NO: 10, except for the native naturally occurring PRO874 polypeptide (SEQ ID NO: 10). Skilled artisans would not recognize the disclosure of SEQ ID NO: 10 as putting appellants in possession of the claimed genus.

Appellants separately argue that claim 15 is adequately described for the same reasons that claims 14, 16, and 17 are adequately described. Appellants further argue that because the genus of polypeptides is smaller than that of claim 14 the board should reverse the rejection of claim 15. Appellants' arguments have been fully considered but they are not persuasive. Claim 15 is not adequately described for the same reasons claim 14 is not adequately described, as discussed above. Although the polypeptides of claim 15 are 99% identical to SEQ ID NO: 10, the specification does not describe any biological activity of the native or naturally-occurring PRO874 polypeptide or any variant thereof. Furthermore, the state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. Skilled artisans would not recognize the disclosure of SEQ ID NO: 10 as putting appellants in possession of the claimed genus.

(9)(e) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 6, 7, 9 and 11–17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Support for the limitations "amino acids 34-321 of SEQ ID NO: 10" (claims 6, 7, and 12–17), "nucleotides 100-966 of the cDNA ..." (claims 6 and 11–17), and "amino acids 81-109 or 232-253 of SEQ ID NO: SEQ ID NO: 10" (claims 6, 9, 12–17) cannot be found in the disclosure as originally filed, which raises the issue of new matter.

(10)(e) Response to Argument

Appellants argue that paragraph 0196 combined with Figure 10 conveys with reasonable clarity that Appellants were in possession of the claimed invention. Applicant's arguments have been fully considered but they are not persuasive. Paragraph 0196 discloses that it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides. However, the species methionine residue #34 as the starting amino acid is not supported by this generic disclosure because there is no express, implicit, or inherent support for this species to the exclusion of all the other species. In other words, the disclosure would not reasonably lead the skilled artisan to this particular species.

Appellants argue that SEQ ID NO: 9 inherently discloses the polypeptides of SEQ ID NO: 10 starting at any of the eight methionine residues, and therefore, Appellants were clearly in possession "... nucleotides 100-966 of the cDNA ...". Applicant's arguments have been fully considered but they are not persuasive for the same reasons that the disclosure would not reasonably lead the skilled artisan to the species methionine residue #34 as the starting amino acid. There is no evidence of record that the naturally occurring PRO874 polypeptide actually starts at methionine residue #34.

Appellants argue that the examiner has misstated the test for compliance with the written description requirement. Applicant's arguments have been fully considered but they are not persuasive. The species methionine residue #34 as the starting amino acid is not supported by the generic disclosure because there is no express, implicit, or inherent support for this species to the exclusion of all the other species. There is no evidence of record that the naturally occurring PRO874 polypeptide actually starts at methionine residue #34. Therefore, the specification does not convey with reasonable clarity that Appellants were in possession of the invention now claimed.

Appellants argue that Figure 10 implicitly discloses the 81-109 and 232-253 fragments of SEQ ID NO: 10 and that the examiner's argument is moot in light of the present claim amendments. Applicant's arguments have been fully considered but they are not persuasive. The specification describes an isolated PRO polypeptide having at least about a recited % "amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein." Page 8, 0014. See also page the paragraph bridging pages 28-29. The specification also describes "an isolated PRO polypeptide which is ... transmembrane domain-deleted" (page 9, 0017). However, the specification does not specifically define the 81-109 and 232-253 fragments of SEQ ID NO: 10 as either intracellular domains or an extracellular domains. Figure 10 discloses four transmembrane domains. Thus, the extracellular domains depend on how the polypeptide is arranged in the membrane. However, the specification does not disclose how the

polypeptide is arranged in the membrane. The disclosure at page 8, paragraph 0014 and at the paragraph bridging pages 28-29 coupled with figure 10 and the newly added claim limitations, imply that the 81-109 and 232-253 fragments of SEQ ID NO: 10 are extracellular domains, which introduces new concepts and violates the description requirement of the first paragraph of 35 U.S.C. 112.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Appellants' APPENDIX B – Evidence

Hu (J Proteome Res. 2003 Jul-Aug;2(4):405-12), Haynes (Electrophoresis. 1998 Aug;19(11):1862-71) and Gygi (Mol Cell Biol. 1999 Mar;19(3):1720-30) were first submitted by Appellants in the Information Disclosure Statement (IDS) filed 07/01/2005.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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